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Portable HEPA Filter Air Cleaner Use during Pregnancy and Children's Cognitive Performance at Four Years of Age: The UGAAR Randomized Controlled Trial

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Background: Developmental exposure to air pollution is associated with diminished cognitive abilities in observational studies, but no randomized controlled trial has examined the effect of reducing air pollution on cognition in children.

Objectives: We sought to quantify the impact of reducing exposure to particulate matter (PM) during pregnancy on children's cognitive performance at 4 y of age.

Methods: In this single-blind, parallel-group, randomized controlled trial in Ulaanbaatar, Mongolia, we randomly assigned 540 nonsmoking pregnant women (268 intervention and 272 control) to receive 1–2 portable high-efficiency particulate air (HEPA) filter air cleaners or no air cleaners. The air cleaners were used from a median of 11 wk gestation until the end of pregnancy. The primary outcome was full-scale intelligence quotient (FSIQ) assessed using the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) when children were a median of 48 months old. We imputed missing outcome data using multiple imputation with chained equations, and our primary analysis was by intention to treat.

Results: After excluding known miscarriages, stillbirths, neonatal deaths, and medical conditions that impeded cognitive testing and imputation, 475 (233 control and 242 intervention) children were included in our analyses. In an unadjusted analysis, the mean FSIQ of children who were randomly assigned to the intervention group was 2.5 points [95% confidence interval (CI): −0.4, 5.4 points] higher than that of children in the control group. After adjustment to account for an imbalance in preterm birth between groups, the effect estimate increased to 2.8 points (95% CI: −0.1, 5.7).

Conclusions: Reducing PM air pollution during pregnancy may improve cognitive performance in childhood. https://doi.org/10.1289/EHP10302

Introduction

Exposure to fine particulate matter ($PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm) air pollution during pregnancy is associated with fetal growth restriction and shorter gestation.[1] In turn, an unfavorable intrauterine environment may alter developmental programming and increase risk of disease and disability later in life.[2] This paradigm is consistent with observational evidence of associations between prenatal exposure to air pollution and impaired neurodevelopment.[3]

Specific mechanisms underlying air pollution's impact on brain development have not been definitively established, but plausible mechanisms have been identified.[4] The prenatal period and the first year of life are key phases in the development of neural networks. The speed and complexity of brain development, combined with the immature detoxification mechanisms in early life, makes the developing brain particularly vulnerable to toxicants. If a toxicant impairs a critical, time-dependent process in the developing brain, there is little chance for repair.[5]

To our knowledge, no study has evaluated whether reducing particle exposure during pregnancy improves children's neurodevelopment. High-efficiency particulate air (HEPA) filter air cleaners ("HEPA cleaners") have been shown to reduce $PM_{2.5}$ concentrations by 29%–82% inside residences, where individuals spend most of their time.[6] In addition, outdoor particles penetrate into buildings, and in many homes most indoor $PM_{2.5}$ is from outdoor sources.[7] Thus, reducing particulate matter (PM) indoors may mitigate the health impacts of outdoor emissions.[8]

Our objective was to evaluate the impact of reducing indoor PM using portable HEPA cleaners during pregnancy on children's cognitive performance at 4 y of age. Specifically, we tested the hypothesis that children born to women randomly assigned to use portable HEPA cleaners during pregnancy would have higher mean cognitive scores at age 4 y than children whose mothers were not assigned to use HEPA cleaners.

Methods

Trial Design

The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study is a single-blind, parallel-group randomized controlled trial (RCT) designed to estimate the effect of portable HEPA cleaner use during pregnancy on fetal growth and early childhood development (ClinicalTrials.gov: NCT01741051). The Simon Fraser University Office of Research Ethics and the Medical Ethics Approval Committee of the Mongolian Ministry of Health approved the study.

Ulaanbaatar, the capital city of Mongolia, has some of the world's worst air quality. The city's population-weighted annual average $PM_{2.5}$ concentration is more than 10 times the World Health Organization (WHO) guideline concentration of 5 $\mu g/m^3$.[9] Approximately half of the Mongolian population lives in Ulaanbaatar, and more than 60% of the city's residents live in neighborhoods consisting of traditional Mongolian felt-lined yurts (gers) and poorly constructed wood or brick homes.[10] Coal emissions from home heating stoves in these neighborhoods account for 45%–70% of the total outdoor $PM_{2.5}$ concentrations in the city.[11] The city's remaining residents live in apartments that receive heat supplied by coal-fired heat and power stations or heat-only boilers.[9]

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Coway provided discounted air cleaners modified for this study. The company had no role in study design, analysis, interpretation, manuscript preparation, or the decision to publish. The authors have no other conflicts of interest to disclose.

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Participants

We recruited participants at two perinatal health clinics in Ulaanbaatar between January 2014 and May 2015. Two study coordinators enrolled 540 pregnant women who met the following criteria: ≥18 y old, ≤18 wk into a single gestation pregnancy, nonsmoker, living in an apartment, not using air cleaner(s) at enrollment, and planning to give birth in a medical facility in Ulaanbaatar. Our original criterion for gestational age at enrollment was 13 wk (first trimester), but shortly after enrollment began, we changed the criterion to 18 wk to increase enrollment. Most participants (81%) enrolled at ≤13 wk. We excluded women living in ger neighborhoods because they have unreliable electricity and gers often have high air exchange, which can make HEPA cleaners less effective. In addition, heating stoves in gers can emit pollution indoors, which could limit generalizability of results.

Study staff obtained written informed consent from each participant before the start of data collection. Participants were compensated up to 325,000 Mongolian tugriks (approximately $130 USD). We prorated compensation depending on the activities that participants completed.

Randomization and Blinding

Study staff confirmed eligibility before participants provided written consent. A study coordinator assigned participants to the control or intervention group at a 1:1 ratio using sealed opaque envelopes containing cards (generated by the principal investigator, R.W.A.) indicating "filter" or "control." After a woman consented to participate, a study coordinator opened the next envelope in the sequence and informed the participant of her assignment. The envelope was then discarded, and the next envelope was opened when the next participant enrolled. Participants were not blinded to their intervention status, but personnel who conducted cognitive testing were blinded.

Intervention

We deployed one or two HEPA cleaners (AP-1009CH; Coway) in the homes of participants in the intervention group. These HEPA cleaners have a clean air delivery rate for tobacco smoke (0.09–1.0 μm particles) of 149 cu ft/m, which is sufficient for rooms of approximately 22 m^2. The control group received no HEPA cleaners. At our request, the manufacturer modified the HEPA cleaners to run at the second-highest fan setting (because of concerns about noise at the highest setting) and disabled a colored light that indicates the particle concentration range. We installed the HEPA cleaners in intervention homes shortly after participants enrolled. We placed an air cleaner in the main living area of all apartments, and in larger apartments (≥40 m^2), we placed a second unit in the participant's bedroom. We encouraged participants to use the HEPA cleaners continuously. We did not replace the HEPA filters during the study, and we retrieved the HEPA cleaners shortly after pregnancy ended.

Prenatal Procedures

During the intervention, we measured $PM_{2.5}$ in participants' homes over two 7-d sampling campaigns using Dylos laser particles counters (DC1700; Dylos Corporation). The early- and late-pregnancy measurements were made at a median of 11 wk and 30 wk gestation, respectively. Full details on the prenatal $PM_{2.5}$ measurement campaigns are provided elsewhere.[12] Participants came to our study office between 5 and 19 wk of pregnancy and again between 24 and 37 wk. At both times we administered a questionnaire to obtain information on family demographics (e.g., parents' ages and education, monthly family income), behavior (e.g., smoking, alcohol consumption), health [e.g., prepregnancy body mass index (BMI)], and previous pregnancies. We also collected a venous whole blood sample during the second visit and analyzed it for lead, mercury, and cadmium concentrations.

We obtained clinic records and recorded birth weight, length, head circumference, gestational age, sex, and mode of delivery. We also used clinic records to identify stillbirths, pregnancy complications, and co-morbidities.[13] The occurrence and timing of spontaneous abortions was self-reported by participants.

Postnatal Procedures

When the children were a median of 15.4 months old (range: 7.7–28.9 months), we invited all living mother–child dyads to reenroll in a follow-up study of postnatal development. At reenrollment we administered a questionnaire on housing and the child's diet, health, and activities since birth. We administered additional questionnaires at 6-month intervals thereafter.

We visited participants' homes annually around the time of the child's birthday. At the same time, we measured $PM_{2.5}$ over 7 d in a convenience sample of participants' homes based on the availability of monitors. During the first postnatal home visit, we also assessed the quality and quantity of nurturing and stimulation using the Home Observation Measurement of the Environment (HOME) assessment.[14]

The mothers and children visited our study office when the children were approximately 2 and 4 y of age. At the 2-y visit we collected a venous whole blood sample from the children for analysis of lead, mercury, and cadmium and administered the matrix reasoning and vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) to the mothers.[15]

Outcomes

During the 4-y visit we measured children's cognitive performance using the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI–IV).[16] The WPPSI-IV is a widely accepted measure of cognitive functioning in children age 2 y and 6 months to 7 y and 7 months. The WPPSI-IV has been used in studies of environmental hazards[17–19] and has been used in Bangladesh,[20] Brazil,[21] China,[18] and Iran.[22] Native Mongolian speakers translated all English WPPSI-IV materials. We refined the WPPSI-IV by piloting it on Mongolian children, updating the translations, and piloting on additional children before assessing the UGAAR cohort. Two Mongolian assessors were trained to administer and score the WPPSI-IV by a co-investigator (DCB) with extensive experience in cognitive testing. Specifically, prior to data collection we conducted a 2-wk in-person WPPSI-IV training session in Ulaanbaatar followed by approximately 3 months of practice testing, which was videotaped and reviewed by the trainer.

We administered 10 WPPSI-IV subtests (information, similarities, block design, object assembly, matrix reasoning, picture concepts, picture memory, zoo locations, bug search, and cancellation) to children at a median age of 48 months (range: 48–51 months). We videotaped the assessments and reviewed them periodically for quality control.

Our primary outcome was full-scale intelligence quotient (FSIQ), which is derived by combining scores from six WPPSI-IV subtests. Our secondary outcomes were verbal comprehension, visual spatial, fluid reasoning, working memory, processing speed, nonverbal, general ability, and cognitive proficiency. FSIQ indicates a child's general intellectual functioning. The other indices provide process-specific measurements.

Sample Size

The UGAAR study was initially focused on fetal growth, so our sample size calculations were based on term birth weight.[13] We estimated that 540 participants were needed, assuming 18% attrition, a type I error rate of 0.05 (2-sided), and a type II error rate of 0.20.

Statistical Analyses

We generated descriptive statistics for maternal baseline characteristics. Calculating composite WPPSI-IV scores requires scaling raw scores using the distribution from a reference population. With no Mongolian reference population, we scaled the distribution of raw scores from the UGAAR cohort to match the mean and standard deviation of the Canadian reference population, which included children 48–91 months old who were assessed from July to August 2012 (Table S1).[16] This approach allowed us to convert raw scores to scaled scores and combine scaled scores into indices according to the WPPSI-IV protocol.

To assess the validity of the WPPSI-IV in this setting we evaluated unadjusted relationships between WPPSI-IV FSIQ scores and established predictors of cognitive performance in young children: preterm birth (PTB, <37 wk),[23] sex,[24] maternal intelligence (mothers' WASI matrix reasoning and vocabulary raw scores),[25] and HOME scores.[26] For binary predictors (PTB and sex), FSIQ effect estimates are expressed as a difference in mean FSIQ scores between children born preterm and full term and between boys and girls. For continuous predictors (WASI and HOME scores), FSIQ effect estimates are reported per interquartile range (IQR) contrast.

Our primary analysis was by intention-to-treat (ITT) and included 475 children (233 control and 242 intervention); a secondary analysis included 383 complete cases. The participants in the ITT analysis comprise the full cohort except those who withdrew prior to baseline data collection ($n=8$), pregnancy losses ($n=46$), neonatal deaths ($n=5$), and children with a medical condition that may affect WPPSI-IV testing or our ability to impute scores [$n=6$; one with Down syndrome, one with a hearing and speech impairment, one with cerebral palsy, and three with autism spectrum disorder (ASD)]. We imputed scores for 92 children who failed to complete one or more WPPSI-IV subtests, assuming data were missing at random. We generated 20 imputed data sets using multiple imputation with chained equations (MICE) (SAS Proc MI and Proc MIANALYZE; SAS Institute, Inc.) after stratifying by treatment group. We included in the imputation model variables associated with missingness and/or FSIQ: child's sex, enrollment season, previous pregnancy, self-reported air cleaner usage and vitamin intake at baseline, father's BMI, mother's alcohol intake during pregnancy, birth term, head circumference at birth, and the completed WPPSI-IV subtest raw scores.

In both our ITT and complete case analyses, we used linear regression to estimate the effect of the intervention on mean WPPSI-IV scores. Five control group participants incorrectly received the intervention, and three intervention participants did not receive HEPA cleaners; we analyzed the data according to original group assignments. We report unadjusted effect estimates and estimates adjusted for PTB because we previously found that the intervention was associated with lower risk of spontaneous abortion and higher risk of PTB.[13] We speculated that the intervention allowed those who otherwise might have died *in utero* to survive but be born preterm.[13] Although PTB may be on the causal pathway, we adjusted for PTB to balance the frequency of PTB between the control and intervention groups. In a preplanned analysis, we also quantified the intervention's effect on FSIQ after stratifying by household smoking behavior.

We also conducted several post hoc analyses. In the ITT analysis we estimated the effect of the intervention on FSIQ after adjusting for child's sex and after excluding eight participants who mistakenly received or did not receive HEPA cleaners. In addition to the intervention's effect on mean WPPSI-IV scores, we were also interested in effects at different parts of the FSIQ distribution. Thus, we used quantile regression to estimate the intervention's effect at each decile of the FSIQ distribution among complete cases.

Role of the Funding Source

This study was funded by the Canadian Institutes of Health Research. Coway provided discounted air cleaners modified for this study. The funder and the company had no role in study design, analysis, interpretation, manuscript preparation, or the decision to publish.

Results

We recruited 540 pregnant women from 9 January 2014 to 1 May 2015 and randomly assigned 272 to the control group and 268 to the intervention group (Figure 1). Participants were enrolled at a median (25th, 75th percentile) of 11 wk (9, 13 wk) gestation in the control group and 11 wk (8, 13 wk) gestation in intervention group. We observed 514 women (253 control and 261 intervention) to the end of pregnancy. There were 46 known pregnancy losses (28 control and 18 intervention), 468 live births (225 control and 243 intervention), and 5 neonatal deaths (1 control and 4 intervention). We enrolled 416 participants (194 control and 222 intervention) into the postnatal study, and 383 children (182 control and 201 intervention) completed the WPPSI-IV between 28 September 2018 and 8 January 2020.

Baseline Characteristics

Baseline characteristics were comparable between intervention and control groups (Table 1; Table S2). The median (25th, 75th percentile) maternal ages at enrollment in the control and intervention groups were 28 y (25, 32 y) and 29 y (25, 33 y), respectively. Approximately half of the women lived with a smoker at enrollment, and about 80% had a university degree.

Pregnancy and Childhood Characteristics

Intervention group participants reported using the HEPA cleaners for a median (25th, 75th percentile) of 70% (60%, 80%) of time during pregnancy.[13] Just under half of the study population reported living with a smoker during pregnancy. Maternal intelligence measured by WASI did not differ between the control and intervention groups (Table 2). Breastfeeding frequency and duration were also similar between groups (Table 2). Maternal blood lead and mercury concentrations measured late in pregnancy were similar between groups, but blood cadmium concentrations were 14% lower [95% confidence interval (CI): 4, 23%] among intervention participants.[12] We obtained information on gestational age at birth for 455 (220 control and 235 intervention) of the children included in the ITT analysis. Among those children, PTB occurred more frequently in the intervention group (24 or 9.9%) than in the control group (13 or 5.6%) (Table 2). Children's blood metals concentrations at 2 y of age were similar between groups, as were HOME inventory total scores. The portion of intervention and control group participants who reported using their own air cleaner after birth was 14% and 17%, respectively. Postnatal air cleaner use was reported by 17% of mothers who completed university and 15% of mothers who did not. Seven percent of families earning <800,000 tugriks per month at baseline reported using an air cleaner after their child's birth.

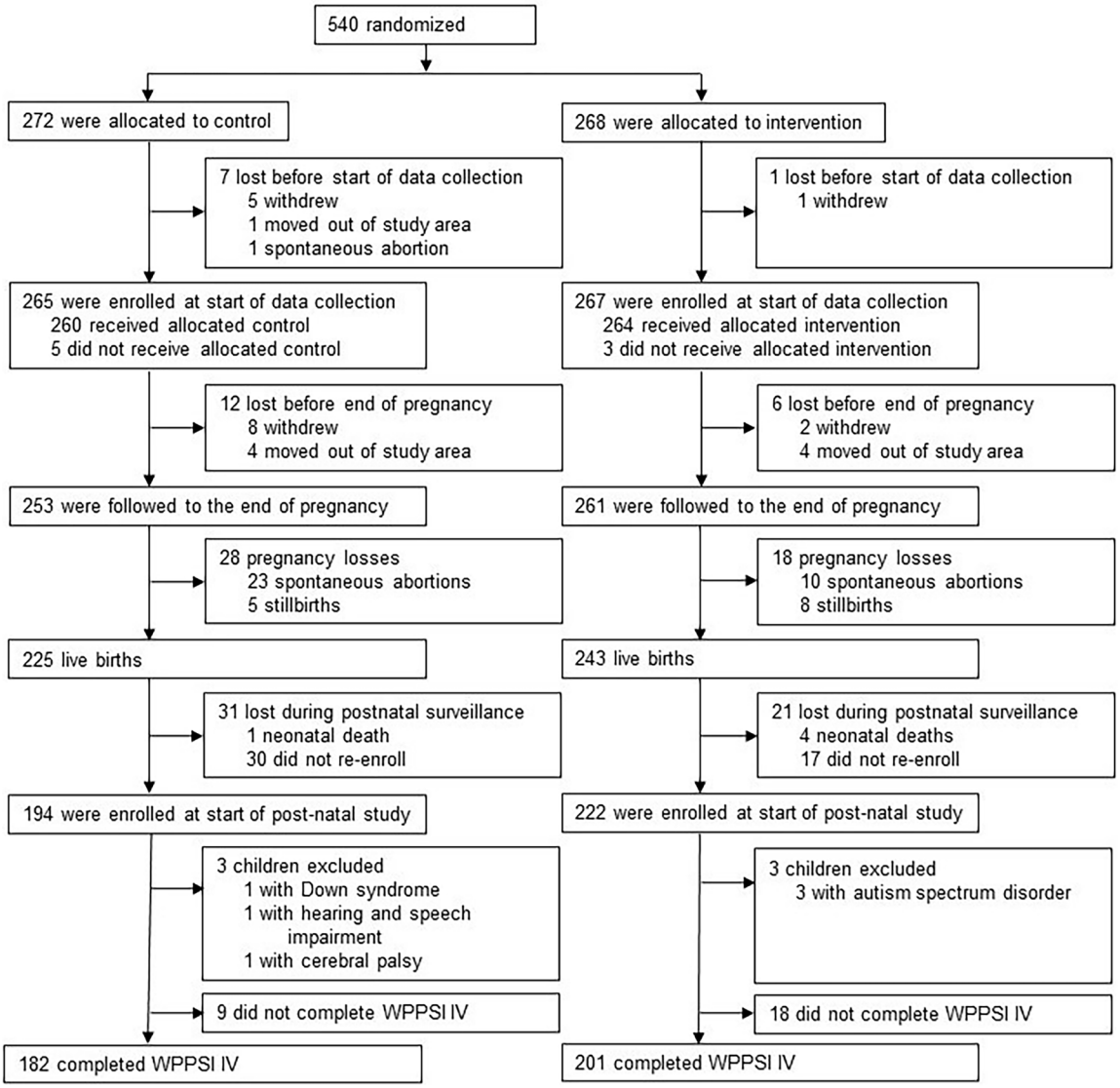

Figure 1. Profile for the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) high-efficiency particulate air (HEPA) filter air cleaner trial in Ulaanbaatar, Mongolia. Note: WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.

Among those who earned more than 800,000 tugriks per month, 17% reported postnatal use of an air cleaner. Mothers of children who did not participate in WPPSI-IV testing were younger, more likely to be in the control group, and more likely to have enrolled in winter in comparison with mothers of those who participated in testing (Table S3).

Pollution Concentrations

We previously reported a difference of 29% (95% CI: 21, 37%) in $PM_{2.5}$ concentrations between groups, with geometric means of 24.5 $\mu g/m^3$ in the control group and 17.3 $\mu g/m^3$ in the intervention group (Table S4).[12] The HEPA air cleaners were removed shortly after pregnancy ended and indoor $PM_{2.5}$ concentrations during childhood were comparable between control and intervention homes (3% lower in intervention homes; 95% CI: −17, 9%).

Correlates of WPPSI-IV Scores

Among complete cases, male sex and PTB were associated with 6.3-point (95% CI: 3.5, 9.1; $n = 383$) and 6.8-point (95% CI: 1.6, 12.0; $n = 382$) lower mean FSIQ scores, respectively. IQR increases in maternal WASI vocabulary and matrix reasoning raw scores were associated with 1.6-point (95% CI: 0.0, 3.3, $n = 363$) and 3.5-point (95% CI: 1.7, 5.3; $n = 363$) higher mean FSIQ scores, respectively. An IQR increase in HOME score was associated with a 3.2-point (95% CI: 1.3, 5.0; $n = 301$) higher mean FSIQ score.

Intervention Effects

In the imputed ITT analysis, children in the intervention group had a 2.5-point (95% CI: −0.4, 5.4) higher mean FSIQ than children in the control group (Table 3). Adjusting for PTB increased the estimate to 2.8 points (95% CI: −0.1, 5.7), and after adjustment for both PTB and child's sex the effect estimate was 3.0 points (95% CI: 0.2, 5.9). Excluding eight participants who incorrectly received or did not receive the HEPA cleaners had little effect on the estimate (2.5 points; 95% CI: −0.5, 5.4).

In the complete case analysis, children in the intervention group had a 2.8-point (95% CI: 0.0, 5.7) higher mean FSIQ score

Table 1. Select baseline variables for participants included in the intention-to-treat analysis of the Ulaanbaatar Gestation and Air Pollution Research trial in Ulaanbaatar, Mongolia, 2014–2015 ($n = 475$).

	Control ($n = 233$)	Intervention ($n = 242$)
	Median (25th, 75th percentile) or n (%)	Median (25th, 75th percentile) or n (%)
Maternal age at enrollment	28 (25, 32)	29 (25, 33)
Not reported [n (%)]	6 (2.6)	6 (2.5)
Weeks pregnant at enrollment	11 (9, 13)	11 (8, 13)
Not reported [n (%)]	8 (3.4)	12 (4.9)
Enrollment season		
Winter	76 (32.6)	72 (29.8)
Spring	73 (31.3)	65 (26.7)
Summer	24 (10.3)	31 (12.8)
Fall	60 (25.8)	74 (30.6)
Marital status		
Married or common law	183 (78.5)	209 (86.4)
Not married or common law	49 (21.0)	33 (13.6)
Not reported [n (%)]	1 (0.4)	0 (0.0)
Lived with a smoker at enrollment		
Yes	117 (50.2)	119 (49.2)
No	111 (47.6)	119 (49.2)
Not reported [n (%)]	5 (2.2)	4 (1.7)
Maternal education		
Completed university	187 (80.3)	193 (79.8)
Did not complete university	31 (13.3)	29 (12.0)
Not reported [n (%)]	15 (6.4)	20 (8.3)
Monthly household income[a]		
≥800,000 Tugrik	182 (78.1)	191 (78.9)
<800,000 Tugrik	46 (19.7)	47 (19.4)
Not reported [n (%)]	5 (2.2)	4 (1.7)
Parity		
0	73 (31.3)	79 (32.6)
1	92 (39.5)	88 (36.4)
≥2	51 (22.0)	62 (25.6)
Not reported [n (%)]	17 (7.3)	13 (5.4)

Note: Percentages may not total 100 due to rounding.
[a]At the time of data collection 800,000 tugriks was equivalent to approximately $360 USD.

Table 2. Select variables measured during pregnancy and after birth for dyads included in the intention-to-treat analysis of the Ulaanbaatar Gestation and Air Pollution Research trial in Ulaanbaatar, Mongolia, 2014–2019 ($n = 475$).

	Control ($n = 233$)	Intervention ($n = 242$)
	Median (25th, 75th percentile) or n (%)	Median (25th, 75th percentile) or n (%)
Maternal characteristics		
Delivery type		
Cesarian	86 (37.0)	85 (35.1)
Vaginal	134 (57.5)	151 (62.4)
Unknown [n (%)]	13 (5.6)	6 (2.5)
Blood lead concentration (μg/dL)	1.46 (1.17, 1.80)	1.43 (1.17, 1.86)
Not measured [n (%)]	61 (26.2)	43 (17.8)
Blood cadmium concentration (μg/L)	0.22 (0.16, 0.31)	0.19 (0.14, 0.28)
Not measured [n (%)]	61 (26.2)	43 (17.8)
Blood mercury concentration (μg/L)	0.31 (0.22, 0.54)	0.30 (0.20, 0.44)
Not measured [n (%)]	61 (26.2)	43 (17.8)
WASI Matrix Reasoning raw score	16.0 (12, 19)	17.0 (13, 19)
Not measured [n (%)]	58 (24.9)	33 (13.6)
WASI Vocabulary raw score	36 (32, 39)	35 (31, 39)
Not measured [n (%)]	58 (24.9)	33 (13.6)
Child characteristics		
Sex		
Female	110 (47.2)	109 (45.0)
Male	112 (48.6)	126 (52.1)
Unknown [n (%)]	11 (4.7)	7 (2.9)
Birth term		
Preterm (<37 wk)	13 (5.6)	24 (9.9)
Term (≥37 wk)	207 (88.8)	211 (87.2)
Unknown [n (%)]	13 (5.6)	7 (2.9)
Season of birth		
Winter	26 (11.2)	35 (14.5)
Spring	51 (21.9)	56 (23.1)
Summer	69 (29.6)	78 (32.2)
Fall	74 (31.7)	66 (27.3)
Unknown [n (%)]	13 (5.6)	7 (2.9)
Breastfed infant		
Never	6 (2.6)	5 (2.1)
<12 months	43 (18.5)	53 (21.9)
≥12 months	139 (59.7)	156 (64.5)
Not reported [n (%)]	45 (19.3)	28 (11.8)
HOME inventory total score	30.0 (28.0, 32.5)	30.0 (27.0, 34.0)
Not measured [n (%)]	76 (32.6)	77 (31.8)
Blood lead concentration at 2 y of age (ug/dL)	2.60 (1.86, 3.63)	2.47 (1.68, 3.47)
Not measured [n (%)]	80 (34.3)	68 (28.1)
Blood cadmium concentration at 2 y of age (μg/L)	0.05 (0.04, 0.08)	0.05 (0.04, 0.08)
Not measured [n (%)]	80 (34.3)	68 (28.1)
Blood mercury concentration at 2 y of age (μg/L)	0.18 (0.13, 0.25)	0.18 (0.13, 0.27)
Not measured [n (%)]	80 (34.3)	68 (28.1)
Child's age at WPPSI-IV assessment (months)	48.0 (48, 48)	48.0 (48, 48)
No WPPSI-IV [n (%)]	51 (21.9)	40 (16.5)
HEPA filter air cleaner usage after birth		
Yes	39 (16.8)	33 (13.6)
No	133 (57.0)	162 (66.9)
Not reported [n (%)]	61 (26.2)	47 (19.4)

Note: Percentages may not total 100 due to rounding. HEPA, high-efficiency particulate air; HOME, Home Observation Measurement of the Environment; WASI, Wechsler Abbreviated Scale of Intelligence; Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.

in an unadjusted analysis and a 3.2-point (95% CI: 0.3, 6.0) higher mean FSIQ after adjustment for PTB (Table 3).

In the ITT analysis, mean scores for secondary outcomes were consistently higher in the intervention group (Table 3). However, only the effect estimates for verbal comprehension had CIs that did not span the null (3.5 points, 95% CI: 0.2, 6.8).

In a stratified ITT analysis, the effect of the intervention on mean FSIQ was 1.9 points (95% CI: −2.1, 5.9) among children whose mothers lived with a smoker at baseline and 3.2 points (95% CI: −0.9, 7.4) among those whose mothers did not live with a smoker. Stratified results among complete cases were similar to those from the ITT analysis for children whose mothers did (2.0 points; 95% CI: −2.0, 6.4) and did not (3.6 points; 95% CI: −0.5, 7.7) live with a smoker. In a post hoc quantile regression analysis of complete cases, the effect of the intervention on FSIQ was more pronounced among children at the lower end of the FSIQ distribution (Figure 2; Table S5).

Discussion

To our knowledge, this study is the first RCT of reductions in air pollution during pregnancy and cognitive performance in childhood. In this cohort of women living in a polluted community, the use of air cleaners from late in the first trimester to the end of pregnancy increased mean FSIQ at 4 y of age by 2.5 points (95% CI: −0.4, 5.4). Estimated effects on mean FSIQ were slightly larger after adjusting for PTB (2.8 points; 95% CI: −0.1, 5.7) and among complete cases (2.8 points; 95% CI: 0.0, 5.7). These results indicate that reducing PM air pollution exposure during pregnancy could be beneficial for cognitive development.

Observational studies suggest that prenatal exposure to ambient air pollution is associated with impaired neurodevelopment at

Table 3. Mean WPPSI-IV composite scores and estimated intervention effects in primary intention-to-treat ($n = 475$) and secondary complete case ($n = 383$) analyses from the Ulaanbaatar Gestation and Air Pollution Research trial in Ulaanbaatar, Mongolia.

	Intention-to-treat analysis				Complete case analysis			
	Mean score (standard deviation)				Mean score (standard deviation)			
	Control ($n = 233$)	Intervention ($n = 242$)	Unadjusted intervention effect estimate (95% CI)	Adjusted intervention effect estimate[a] (95% CI)	Control ($n = 182$)	Intervention ($n = 201$)	Unadjusted intervention effect estimate (95% CI)	Adjusted intervention effect estimate[a] (95% CI)
Full scale IQ	97.3 (15.2)	99.8 (13.9)	2.5 (−0.4, 5.4)	2.8 (−0.1, 5.7)	97.3 (14.9)	100.1 (13.5)	2.8 (0.0, 5.7)	3.2 (0.3, 6.0)
Verbal comprehension	97.3 (16.5)	100.8 (16.1)	3.5 (0.2, 6.8)	3.8 (0.4, 7.1)	97.4 (15.8)	101.2 (15.5)	3.8 (0.6, 6.9)	4.2 (1.1, 7.4)
Visual spatial	94.5 (16.3)	95.6 (15.1)	1.0 (−2.4, 3.9)	1.2 (−1.9, 4.3)	94.5 (15.7)	95.7 (14.5)	1.2 (−1.8, 4.2)	1.3 (−1.8, 4.4)
Fluid reasoning	97.7 (16.9)	98.5 (17.0)	0.8 (−2.5, 4.1)	1.0 (−2.3, 4.3)	97.8 (16.4)	98.8 (16.6)	0.9 (−2.4, 4.3)	1.0 (−2.3, 4.3)
Working memory	103.0 (15.1)	104.3 (14.3)	1.3 (−1.5, 4.2)	1.4 (−1.5, 4.3)	103.1 (14.5)	104.5 (13.3)	1.4 (−1.4, 4.2)	1.5 (−1.3, 4.4)
Processing speed	99.0 (14.1)	99.6 (13.7)	0.6 (−2.2, 3.4)	0.7 (−2.0, 3.5)	99.0 (13.6)	99.9 (13.1)	0.9 (−1.7, 3.6)	1.1 (−1.6, 3.8)
Nonverbal	97.8 (15.8)	99.1 (14.7)	1.4 (−1.6, 4.3)	1.6 (−1.4, 4.5)	97.8 (15.5)	99.5 (14.1)	1.7 (−1.3, 4.7)	1.9 (−1.1, 4.8)
General ability	96.9 (15.9)	99.6 (14.7)	2.6 (−0.4, 5.8)	3.0 (−0.2, 6.1)	97.0 (15.4)	99.9 (14.2)	2.9 (−0.1, 5.8)	3.2 (0.2, 6.2)
Cognitive proficiency	101.5 (15.0)	102.6 (13.8)	1.1 (−1.7, 3.9)	1.3 (−1.5, 4.1)	101.5 (14.5)	102.9 (13.0)	1.4 (−1.4, 4.1)	1.4 (−1.2, 4.3)

Note: CI, confidence interval; WPPSI-IV, Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.
[a]Adjusted for preterm birth.

3–5 y of age.[3] Several studies also suggest that exposure to airborne polycyclic aromatic hydrocarbons (PAHs) plays a key role. A 2015 meta-analysis, which incorporated 31 studies of children age 6 months to 17 y, concluded that there is sufficient evidence of a causal association between developmental PAH exposure and reduced global IQ in children.[27] A magnetic resonance imaging study reported an association between third trimester exposure to PAHs and reductions in white matter surface among children 7–9 y of age.[28] Particle-bound PAHs are found mostly in the $PM_{2.5}$ size range.[29] The $PM_{2.5}$ in Ulaanbaatar comes primarily from coal combustion, a major source of PAHs.

Consistent with two observational studies, we found significantly greater mean verbal comprehension index scores among children in the intervention group. In an Italian birth cohort study, investigators administered the Wechsler Intelligence Scale for Children (Third Edition) when children were 7 y old and found that exposure during pregnancy to nitrogen dioxide, a marker of traffic emissions, was associated only with lower mean verbal IQ and verbal comprehension index scores.[30] In a U.S. study of 4- to 6-y-old children administered the Stanford Binet Intelligence Scales (Fifth Edition), Loftus et al.[31] reported that PM_{10} exposure during pregnancy was associated with both verbal IQ and nonverbal IQ, but that associations with verbal IQ were stronger and more precise. Collectively, these studies suggest that verbal skills may be particularly sensitive to air pollution exposure.

Because air pollution is ubiquitous, with more than 90% of the world's population breathing $PM_{2.5}$ concentrations above the WHO guideline of $5\ \mu g/m^3$, the population-level impacts of air pollution on brain development could be substantial even if the individual-level effects are modest.[32] Modest changes in cognitive development can also have economic impacts; for example, studies in the United States have estimated that a 1-point reduction in IQ reduces annual earnings by an average of up to 3%.[33]

The randomized deployment of HEPA cleaners in this study provides two important insights. First, because HEPA cleaners reduce particle concentrations more than gases, our results indicate that particle exposure independently affects cognitive development. Second, because exposure during pregnancy is often correlated with exposure after birth, it is difficult in observational studies to evaluate the specific impacts of prenatal exposure.[34] In our trial, however, participants used the air cleaners only until the end of pregnancy, so $PM_{2.5}$ concentrations were 29% lower among intervention participants during pregnancy but similar during childhood.[12] Therefore, our results suggest that reducing PM exposure during pregnancy improves cognitive development in childhood.

Our estimated difference of 2.5 to 3.2 points in mean FSIQ is comparable to the impact of more widely recognized factors affecting neurodevelopment. For example, late PTB (34–37 wk) is estimated to reduce mean FSIQ by 3.6 points,[35] and the long-term impact of mild traumatic brain injury in childhood on mean FSIQ is approximately 4.5 points.[36] In a pooled analysis of lead exposure and IQ, we reported that an increase in blood lead concentration from 2.4 to 10 $\mu g/dL$ was associated with a 3.8-point reduction in IQ among 5- to 10-y-old children.[37]

This study was motivated primarily by observational evidence linking outdoor air pollution with neurodevelopment, but nearly half of the women lived with a smoker at enrollment. In a stratified ITT analysis, we found that the effect of the intervention on FSIQ was more pronounced among children whose mothers did not live with a smoker at baseline. Thus, the benefits of the intervention were probably not primarily due to reductions in exposure to secondhand smoke.

A post hoc quantile regression analysis suggested that the intervention may be most beneficial among children at the lower end of the FSIQ score distribution. Quantile regression has not

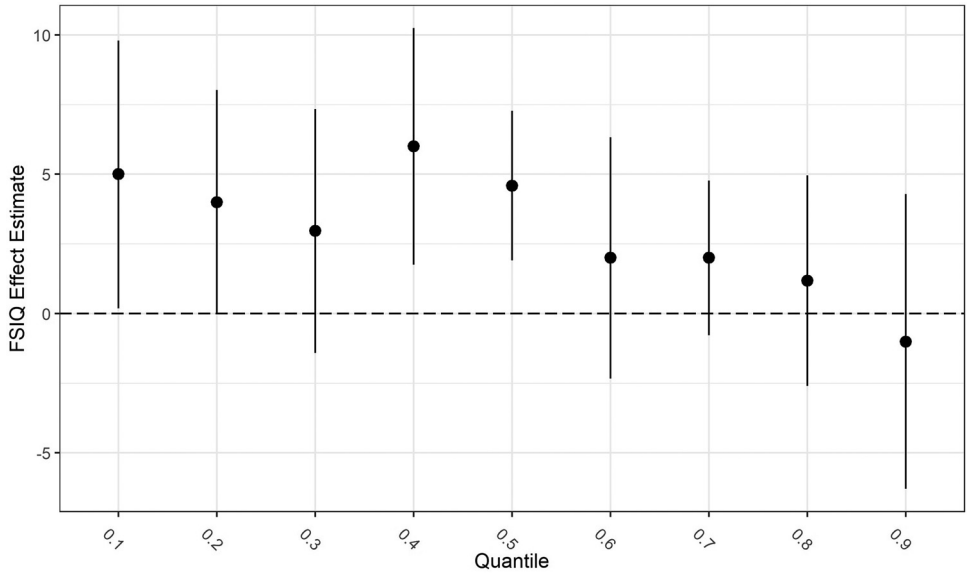

Figure 2. Estimated effects of the intervention on full-scale IQ (FSIQ) from an unadjusted complete case ($n = 383$) quantile regression analysis. Dots represent the point estimate of the intervention's effect on a given quantile of the FSIQ distribution, and lines represent 95% confidence intervals around that estimate. Full reporting of corresponding values is provided in Table S5.

been widely used in studies of pollutants and neurodevelopment. In a study of children's blood lead levels before age 3 y and Wisconsin Knowledge and Concepts Exam (WKCE) scores, effect estimates of lead exposure on reading and math performance scores were greater at the lower end of the math and reading score distributions.[38] In contrast, a study of early-life cadmium exposure and WPPSI scores in Bangladesh found similar associations across the distribution of scores.[19]

Our study had some limitations. The sample size was based on term birth weight, the original outcome of the study, so we may have been underpowered to identify differences in mean FSIQ. Power was further limited by the relatively modest 29% reduction in geometric mean indoor $PM_{2.5}$ concentrations. We excluded ger households because ger neighborhoods have unreliable electricity, and gers often have higher indoor pollution emissions, which could limit generalizability of results. This exclusion may have also limited our exposure gradient. We measured indoor $PM_{2.5}$ as a proxy for personal exposure, and although the intervention reduced residential concentrations, reductions in exposure were likely attenuated by exposure in other locations.[6] FSIQ has been criticized, especially when used in culturally and racially heterogenous settings. Despite its limitations, FSIQ was an appropriate primary outcome in this study of a relatively ethnically and culturally homogenous population. Moreover, we were interested in comparing mean scores between groups, not diagnosis or quantifying the abilities of individual children. Further, there is still much uncertainty on the specific brain regions and functions that are most impacted by air pollution.[39] Therefore, despite its limitations, we determined that using a summary measure, like FSIQ, in this experimental study design was more useful than measures of specific neurodevelopmental domains.[40] Conducting standardized cognitive testing in young children is inherently challenging. Performance on these tests can be influenced by the child's level of interest and engagement. Although this may have contributed random error in our outcome variables, those errors would likely be nondifferential and lead to an underestimation of the intervention's effect.

We are not aware of any previous studies that used the WPPSI-IV in Mongolia. We translated the WPPSI-IV and refined the translations based on pilot testing in Mongolian children before collecting data from UGAAR participants. There is no Mongolian reference population, so we scaled the raw scores to match those of the Canadian reference population then calculated scaled scores and composite indices. Any errors in WPPSI scores introduced by this procedure were likely nondifferential. In addition, we found that PTB, sex, maternal intelligence, and HOME scores were all associated with WPPSI-IV scores, which gives us more confidence in the validity of our outcome measurements.

We did not blind participants with sham air cleaners. This methodological choice may have contributed to a higher frequency of withdrawal among control participants, which in turn may have led to selection bias. The estimated intervention effects were attenuated in the ITT analyses in comparison with the complete case analyses. Because mothers were aware of their intervention status during pregnancy, it is possible that those who received the air cleaners during pregnancy interacted differently with their children, which could have influenced development. This possible change in mother-child interaction is unlikely, however, because HOME scores, which indicate the quality of a child's home environment, were similar in intervention and control homes. The assessors who administered the WPPSI-IV were blinded to participants' treatment group assignments, so information bias is unlikely.

Our results might have been affected by the live birth bias, a form of selection bias that can occur in birth cohort studies of childhood outcomes, which are measured only among live-born children.[41] We previously reported a lower risk of spontaneous abortion among participants in the intervention group.[13] Thus, we may have underestimated the benefits of this intervention if an unmeasured exposure both increased the risk of fetal death and reduced WPPSI-IV scores.[41] Because the difference in spontaneous abortions contributed to differences in PTB,[13] we attempted to account for some of this bias by adjusting for PTB in regression models. This adjustment corrected the imbalance in PTB between treatment groups, but it also blocked any effect of the intervention on WPPSI-IV scores that is mediated by PTB.

We did not include in the ITT analysis six children with medical conditions that could affect WPPSI-IV performance and the reliability of imputed scores. Three children had conditions with no plausible link to air pollution, but three children from the intervention group had been diagnosed with ASD, which has

been associated with air pollution.[42] Although withholding these children from the imputation may have introduced some bias, imputation of WPPSI-IV scores for these children would be unreliable because ASD is a heterogenous disorder and the relationship between ASD and FSIQ varies widely. For example, estimates of the prevalence of intellectual disability (FSIQ <70) among school-age children with ASD range from 11% to 65%, and a substantial fraction of children with ASD have average or above-average intelligence.[43] In addition, children with ASD often have very pronounced strengths and weaknesses on subtests,[44] so standard tests like the WPPSI-IV and summary measures like FSIQ may have limited value for characterizing the cognitive abilities of these children.[45]

Our results indicate that reducing air pollution exposure during pregnancy improved cognitive performance in 4-y-old children. In much of the world, air pollution will threaten public health for the foreseeable future. Portable air cleaners may help to reduce the neurodevelopmental impacts of air pollution until emissions can be brought under control.

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